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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,011	07/16/2003	Julie D. Saba	200116.405C1	1654

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,011	SABA, JULIE D.	
	Examiner	Art Unit	
	Iqbal Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-7 and 12-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-, and 12-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 05/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a CIP of US application 10/348,052 filed 01/17/2003 and 10/053510 filed 1/17/2002 and US Patent 6,830,881, which claim benefit of provisional application 60/349,582 filed on 1/17/2002.

The preliminary amendment filed on 3/10/2006 is acknowledged. Claims 8-11 have been cancelled. Claims 1-7, and 12-31 are at issue and are present for examination.

Applicant's election without traverse of Group I claims 1-31, drawn to a method for identifying an agent that modulates sphingolipid metabolism comprising altered growth of the mutant yeast strain and a decrease of SPHK1 activity and methods utilizing a null mutant of the DPL1, LCB4 and YSR2 genes in the communication filed on 3/10/2006 is acknowledged.

Claims 1-7, and 12-31 are at issue and are present for examination.

Priority

Acknowledgement is made of applicants claim for US application 10/348,052 filed on 01/17/2003 and 10/053510 filed on 1/17/2002 and US Patent 6,830,881, which claim benefit of provisional application 60/349,582 filed on 1/17/2002.

Claim Objections

Claims 2-7,13, 15, 17-19, 21, 23-26, and 28-31 are objected to; as abbreviations should not be used without at least once fully setting forth what they are used fore, such as "DPL1" "LCB4", "SPHK1", "LCBP", "S-1-P", and "YSR2". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, and 12-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a method of identifying an agent that modulates sphingolipid metabolism by culturing a mutant Saccharomyces cerevisiae strain comprising null allele of at least one gene encoding any DPL1 or LCB4 or YSR2 gene or transforming said mutant strain comprising expressing a genus of DNA molecule encoding any polypeptide SPHK1. The specification teaches the structure of only several representative species of such DNAs. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding DPL1 or LCB4 or YSR2 and SPHK1 proteins. Given this lack of description of representative species encompassed by the genus of DNAs used in the methods of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-7, and 12-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying an agent that modulates

sphingolipid metabolism using a mutant Saccharomyces cerevisiae strain comprising a null allele of the endogenous DPL1 gene and/or LCB4 gene and/or YSR2 gene and transforming said mutant strain with the human SPHK1 gene, does not reasonably provide enablement for a method of identifying an agent that modulates sphingolipid metabolism by culturing any mutant yeast strain comprising a null allele of any gene encoding a component a sphingolipid pathway or any DPL1 gene or any LCB4 gene or any YSR2 gene and expressing any gene encoding a non-endogenous sphingolipid pathway component. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-7, and 12-31 are so broad as to encompass a method of identifying an agent that modulates sphingolipid metabolism by culturing any mutant yeast strain comprising a null allele of any gene encoding a component a sphingolipid pathway including any DPL1 gene or any LCB4 gene or any YSR2 gene and expressing any gene encoding a non-endogenous sphingolipid pathway component. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of endogenous and non-endogenous sphingolipid pathway genes including all DPL1 or LCB4 or YSR2 and SPHK1 genes broadly used and modified in the methods of the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequences of only a few mutant S. cerevisiae strains useful within the claimed methods.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims which encompass a method of identifying an agent that modulates sphingolipid metabolism by culturing any mutant yeast strain comprising a null allele of any gene encoding a component a sphingolipid pathway including any DPL1 gene or any LCB4 gene or any YSR2 gene and expressing any gene encoding a non-endogenous sphingolipid pathway component because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting its activity; (B) the general tolerance of polypeptides to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any polypeptides residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope

of the claims broadly including a method of identifying an agent that modulates sphingolipid metabolism by culturing any mutant yeast strain comprising a null allele of any gene encoding a component a sphingolipid pathway including any DPL1 gene or any LCB4 gene or any YSR2 gene and expressing any gene encoding a non-endogenous sphingolipid pathway component. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a method of identifying an agent that modulates sphingolipid metabolism by culturing any mutant yeast strain comprising a null allele of any gene encoding a component a sphingolipid pathway including any DPL1 gene or any LCB4 gene or any YSR2 gene and expressing any gene encoding a non-endogenous sphingolipid pathway component to use in the claimed methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 12, 13, 14-15, 16-19, 20-21, 22-26, and 27-31 are rejected under 35 U.S.C. 103(a) as being obvious over Lanterman et al. (Biochem J. 1998 Jun 1; 332 (Pt 2): 525-31), Kim et al. (Genetics. 2000 Dec; 156(4): 1519-29) and in view of Melendez et al. (Gene. 2000 Jun 13; 251(1): 19-26 and GenBank Accession No. AF266756, created 6/1/2000). Lanterman et al. teach a method of identifying an agent using yeast strain by measuring the production of sphingosine-1-P, which reflects the activity of sphingosine kinase, whether the kinase is inhibited or not in presence or absence of the candidate agent. Lanterman et al. also teach the creation of mutant strain, which comprises a null allele of DPL1 (dihydrosphingosine phosphate lyase) gene and an active LCB4 (kinase of sphingolipid pathway). Lanterman et al. further teach that the ΔDPL mutant yeast is extremely sensitive to sphingosine owing to its inability to degrade S-1-P and in presence of extracellular D-erythro-sphingosine results in accumulation of S-1-P, which is toxic to the cells and inhibits cell growth. However, double

mutants of Δ DPL and Δ LCB4 do not have growth inhibitory effect of extracellular D-erythro-sphingosine because kinase mutant yeast strain comprising Δ LCB4 does not produce S-1-P molecule. It would have been obvious to one of ordinary skill in the art to use this system to identify an agent, which would inhibits kinase which produces S-1-P as Lanterman et al. clearly show that the Δ DPL1 are growth inhibited only in the presence of an active sphingosine kinase. Lanterman et al. do not teach mutant yeast strain comprising null allele of endogenous YSR2 phosphatase gene and transforming said mutant strain with non-endogenous human SPHK1 gene encoding human sphingosine kinase 1, which is complimentary to LCB4 of yeast sphingosine kinase, which is mutated in the mutant yeast strain and expressing said SPHK1 gene.

Kim et al. disclose a method of analyzing sphingolipid metabolism in a mutant S. cerevisiae having disruption mutants of DPL1 (lyase), or LCB4 (kinase), or YSR2 (phosphatase) or in combination and assay methods of sphingolipid metabolism. Kim et al. also disclose that when DPL1 and YSR2 genes are mutated in yeast strain results in the enhancement of sphingosine-1-phosphate (S-1-P) level either in the culture medium or inside the cell to growth inhibitory levels but that Δ DPL1-LCB4-YSR2 triple mutant does not accumulate toxic levels of S-1-P. Kim et al. further teach that over expression of LCB4 i.e. kinase in triple mutant yeast strain Δ DPL1-LCB4-YSR2 results in the 500 fold accumulation of S-1-P than control, which is also extremely growth inhibitory to the mutant cells comprising triple mutant Δ DPL1-LCB4-YSR2 yeast strain, but over-expression of LCB4 in wild type yeast strain do not have such effects. As such Kim et al. clearly show that the triple mutant strains growth inhibited only in the presence of an active heterologous sphingosine kinase gene. Kim et al. do not teach method of screening agents by using mutant yeast system and transforming said mutant strain with non-

endogenous human SPHK1 gene encoding human sphingosine kinase 1 and expression.

Melendez et al. teach a human sphingosine kinase (SPHK1), molecular cloning, and expression in host cells, functional characterization and tissue distribution. Melendez et al. also teach that sphingosine-1-phosphate (SPP), the product of sphingosine kinase, is an important signaling molecule with intra- and extracellular functions. Melendez et al. further teach an assay method to identify an inhibitor such as D,L-threo-dihydrosphingosine or N,N-dimethyl-sphingosine, which inhibit the human SPHK1 kinase and subsequently alter the sphingolipid metabolism.

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Lanterman, Kim and Menendez et al. to assay for inhibitors of human sphingosine kinase 1 (SPHK1) gene to identify an agent by using mutant ΔDPL1 and ΔLCB4 or a ΔDPL1, YSR2, LCB4 yeast strain transformed with said human SPHK1 gene, which modulates sphingolipid metabolism by monitoring either 1) the growth of mutant ΔDPL1, ΔLCB4 or ΔDPL1, YSR2, LCB4 yeast strain, as Lanterman et al. and Kim et al. each show that these strains are growth inhibited in the presence of an active sphingosine kinase such as SPHK, or 2) the concentration of S-1-P, which would decrease if the agents were active. It would have been obvious to one of ordinary skill in the art to identify an agent which alters the growth of mutant yeast strain or accumulation S-1-P concentration to identify an agent would be expected to prevent human diseases like cancer and muscular disorders in which S-1-P enhances cell proliferation, calcium mobilization or Raf/MEK/ERK signaling pathway or decreases apoptosis.

One of ordinary skill in the art would have been motivated to use human sphingosine kinase 1 (SPHK1) gene instead of yeast sphingosine kinase gene in order to obtain an agent or modulator of the human sphingosine kinase to use that agent as a therapeutic measure against human diseases like cancer and muscular disorders.

One of ordinary skill in the art would have a reasonable expectation of success because use of non-endogenous human gene to isolate agents or modulators, in a mutant yeast strain having disruption of endogenous genes are customary and widely used in the art.

Conclusion

Status of the claims:

Claims 1-7, and 12-31 are pending.

Claims 1-7, and 12-31 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

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